REMARKS

Claims 2-4, 8-13, 16, 17 and 19-25 are pending in the present application. Claims 10, 12, 13 and 17 have been withdrawn from consideration as drawn to a non-elected invention, therefore these claims are canceled without prejudice in this amendment. Claim 25 also has been canceled. Applicants note with appreciation that the claims of Groups I and II have been examined on the merits. Although the Office Action Summary indicates that claims 2-4, 8, 9, 11, 16 and 19-25 are allowed, Applicants are proceeding on the assumption that this statement was made in error because these claims were rejected in the body of the Office Action.

Claims 19, 2, 4, 8, 9, 11, 16 and 20-24 have been rejected under 35 U.S.C. § 112, first paragraph on the grounds that the specification is enabling only for preparation and use of compounds wherein R1 is piperidine or piperazine and R2 is 2, 4, 6, trisubstituted phenyl. Applicants have amended the claims to limit the compounds to those in which R1 is piperidine or piperazine which may be substituted or unsubstituted and in which R2 is 2, 4, 6-trisubstituted phenyl. Applicants reserve the right to prosecute the canceled subject matter in one or more divisional applications.

As indicated and taught in the specification, at page 11, first paragraph, R1 groups may be substituted. Preferred substituents for substituted R1 groups as listed on page 11 and claimed in original claim 19 are C_1-C_8 alkyl, C_1-C_3 alkoxy, hydroxy, carboxyl, sulfonyl, nitro, cyano, oxo, halogen or a combination thereof. This disclosure includes the combination of C_1-C_8 alkyl and carbonyl (C_1-C_8 alkoxycarbonyl). These specifically disclosed embodiments are claimed in the amended claims (claims 19 and 27).

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Applicants respectfully submit that the specification fully enables the production and use of all compounds encompassed by the amended claims and that these amendments fully overcome the rejection of these claims under 35 U.S.C. §112, first paragraph. Applicants therefore request that the rejection of claims 19, 2, 4, 8, 9, 11, 16 and 20-24 be withdrawn.

Claim 19 has been rejected under 35 U.S.C. § 112, second paragraph on the grounds that it is indefinite. The Office has noted the particular language "any radicals," "unsubstituted or substituted," "general," "heteroaliphatic ring" and "in particular." Claim 25 also is indicated to be a substantial duplicate of claim 3. Applicants have amended claim 19 to avoid the language deemed unclear by the Office, canceled claim 25 and added new claims 26 and 27. Claim 27 is directed to the L enantiomer of Nα (2,4,6-triisopropylphenylsulfonyl)-3-amidino-phenylalanine ethoxycarbonylpiperazide. New claim 26 is a rewritten version of canceled claim 25 in independent form which claims the L-enantiomer. This new claim is supported by the original disclosures, in particular original claim 18. In addition, claims 4 and 16 have been amended to delete language objected to by the Office and to correct a minor, obvious typographical error. Applicants believe that these amendments fully address each of the points noted in the Office Action. The claims are believed to comply with 35 U.S.C. § 112, second paragraph and therefore Applicants request that this rejection be withdrawn.

Claims 19, 2-4, 11, 16, 23 and 24 have been rejected under 35 U.S.C. § 102(a) as anticipated by Wikstroem et al. and under 35 U.S.C. § 103(a) as obvious over Wikstroem et al. The Wikstroem et al. reference, or the patent upon which it is based, appears to be

dated July 15, 1999. As the Office has recognized, this reference is dated subsequent to the priority date for this application, which is July 20, 1998. Applicants are submitting, with this response, an English translation of a certified copy of the priority document EP 98113519.7, together with a signed statement that the translation of the certified copy is accurate. Support for the general formula I may be found on pages 6-11 of the translated document. Preferred compounds are taught, for example, on page 13, second full paragraph. Under 37 C.F.R. § 1.55, this submission allows the application to rely upon the priority documents and removes the Wikstroem et al. reference as prior art. Applicants therefore request that the rejection of claims 19, 2-4, 11, 16, 23 and 24 under 35 U.S.C. § 102(a) and under 35 U.S.C. § 103(a) be withdrawn.

Claims 19, 2, 4, 16 and 20-24 have been rejected under 35 U.S.C. § 103(a) as obvious over the Sturzebecher et al. references (J. Med. Chem., 1997 and WO 94/18185). The Office states that Sturzebecher et al. teach a group of piperazides of 3-amidinophenylalanine derivatives in Table 4, p. 3094 of the J. Med. Chem. article. In particular, the Office Action describes compounds 2-6, 15, 17 and 27 of Sturzebecher as differing from the claimed compounds only as to R2, which is naphthyl. From these asserted disclosures, the Office concludes that a person of ordinary skill in the art would have been motivated to select the claimed compounds.

The present claims are specifically directed to a method of treating a urokinase-associated or urokinase receptor-associated disorder in a patient. To make out a case of prima facie obviousness against these or any claims, the Office must meet three criteria: (1) the cited prior art reference must teach or suggest

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each and every element of each rejected claim, (2) there must be motivation to modify what is fairly disclosed or suggested in the reference to achieve the claimed invention, and (3) there must be a reasonable expectation of success. M.P.E.P. § 2143. Applicants respectfully submit that the Office cannot make out a case of prima facie obviousness with respect to the invention of this application based on the Sturzebecher et al. references.

Neither Sturzebecher et al. reference above, nor the references in combination, teach, suggest, or even hint at the method of treating a urokinase-associated or urokinase receptor-associated disorder. The disclosures relate to thrombin-inhibiting anticoagulant compounds and do not teach or suggest to one of ordinary skill that the method of the present claims should be performed or even could be performed. The disclosures of Table 4, cited by the Examiner, teach away from such use of the compounds by indicating very low inhibition of urokinase (UK) for the compounds. See Sturzebacher et al., J. Med. Chem. p. 3094. Therefore, the disclosures of the cited references completely lack teaching or suggestion of at least one element of the rejected claims. In addition, the amendment, made herein, to define R1 as a trisubstituted phenyl residue further distinguishes the claimed invention from the compounds disclosed by Sturzebecher et al. Applicants submit that no fair interpretation of the teachings and suggestions of Sturzebecher et al. could lead the skilled person to the invention of this application.

Further, there can be no motivation to alter the teachings of Sturzebecher et al. to achieve the treatment methods claimed here because these authors have indicated that the urokinase-inhibiting activity of their disclosed compounds is limited. Sturzebecher et al. therefore suggest to the skilled person that an attempt to

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treat a urokinase-related disorder would be futile. This teaching also eliminates any reasonable expectation of success even if the attempt were made.

Applicants therefore believe that the Office cannot meet even one of the necessary criteria for making out a prima facie case of obviousness against the present claims based on the Sturzebecher references. Withdrawal of the rejection of claims 19, 2, 4, 16 and 20-24 under 35 U.S.C. § 103(a) is respectfully requested.

Applicants recently have discovered a 1998 Pentapharm Product Catalog, which is submitted in an Information Disclosure Statement with this response. Applicants request that the Examiner consider the disclosures of this reference with respect to the present application. This reference discloses Nα(2,4,6-triisopropyl-phenylsulfonyl)-3-amidino-(L)phenylalanine-4-ethoxycarboxyl-piperazidehydrochloride (designed as PeFa-0888; Pefabloc® UPA) for application as a "low molecular weight synthetic inhibitor for urokinase (uPA)." Applicants submit that the compounds listed in this catalog are intended only as protease inhibitors for research and industrial processes. There is absolutely no teaching or suggestion, or even a hint that these compounds could be used as medicinal products for treating urokinase-associated or urokinase receptor-associated disorder in a patient, much less any experimental data or evidence pertaining to this use. In particular, there is no evidence that the compounds claimed in the methods of this invention could be used in this context, i.e., that they are not cytotoxic in pharmacologically effective concentrations (see specification, Example 5), that they inhibit the proteolytic activity of tumor cells (see specification, Example 6) or that they exhibit an in vivo effectiveness in an animal model (see specification, Examples 7 and 8).

The disclosures of the Pentapharm Catalog therefore do not teach or disclose the method that is claimed here because they completely lack any suggestion or hint that the listed compound could be used as is required by the claims presented here. Furthermore, by no stretch of the imagination could the disclosures or fair suggestion of this catalog list be construed as enabling the claimed method of treating urokinase related disorders in a patient for the skilled person. An enabling disclosure for the pharmaceutical method of the claimed invention was made only in the context of the data first disclosed in the present specification. Therefore, only with impermissible hindsight and reference to the instant specification could the skilled person achieve the present invention or derive the motivation to attempt the present invention with a reasonable expectation of success. Applicants therefore submit that the present claims are patentable over this reference.

In view of the foregoing amendments and remarks, Applicants respectfully submit that the claims are in condition for allowance and request favorable action at this time.

<table>
<tr><td colspan="6">RESPECTFULLY SUBMITTED,</td></tr>
<tr><td>NAME AND REG. NUMBER</td><td colspan="5">Martha Cassidy, Registration No.: 44,066</td></tr>
<tr><td>SIGNATURE</td><td colspan="3"></td><td>DATE</td><td>2/11/03</td></tr>
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<tr><td>COUNTRY</td><td>U.S.A.</td><td>TELEPHONE</td><td>202-783-6040</td><td>FAX</td><td>202-783-6031</td></tr>
</table>

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APPENDIX

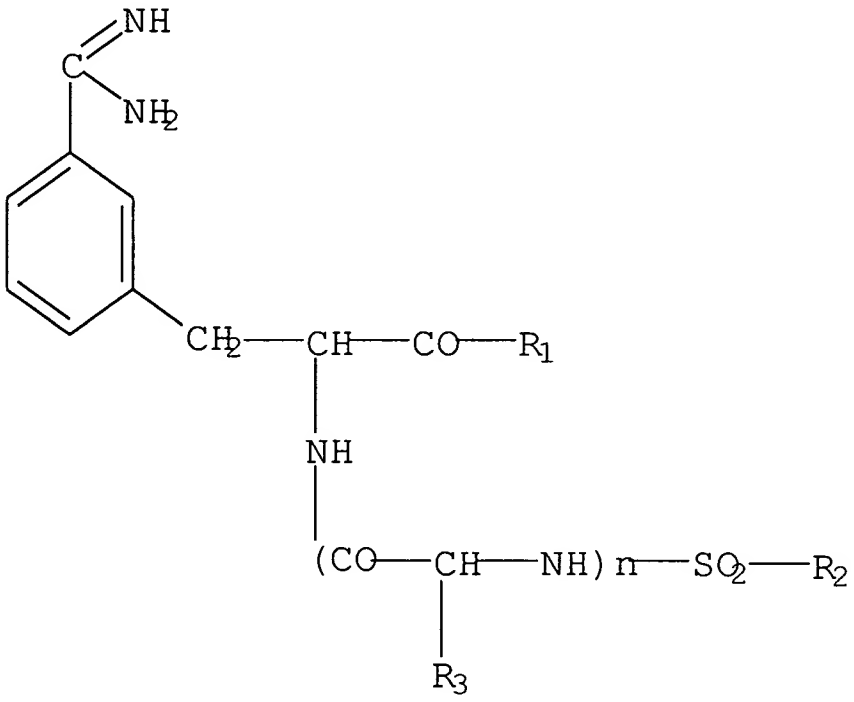
Marked-Up copy of claims to show amendments:

3. (Twice Amended) The method of claim 19, wherein [the] said compound of [the] formula I is Nα-(2,4,6-triisopropylphenylsulfonyl)-3-amidino-(D,L)-phenylalanine 4-ethoxycarbonylpiperazide[, is the L enantiomer] or a pharmaceutically suitable salt [of one of the compounds] thereof.

4. (Thrice Amended) The method of claim 19, characterized in that the compounds are present in the form of physiologically acceptable acid salts[, in particular as hydrochlorides].

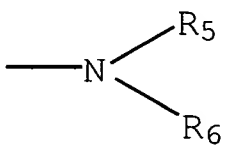
16. (Twice Amended) A method for inhibiting urokinase in living creatures[, in particular in humans,] by administering an effective quantity of at least [on eurokinase] one urokinase inhibitor as claimed in claim 19.

19. (Amended) A method of treating a urokinase-associated or urokinase receptor-associated disorder in a patient in need of such treatment, [said treatment] comprising administering to the patient a therapeutic amount of a compound of formula I



which [are] <u>is</u> present as [racemates and also] <u>a racemate or</u> as D- or L- [configured compounds] <u>enantiomers</u> and in which

R^1 [(a) is OH or OR^4, where R^4 is unsubstituted or substituted, branched or unbranched C_1-C_8-alkyl, C_3-C_8-cycloalkyl or aralkyl,

(b) represents a group of the formula 

in which R^5 and R^5 are any radicals, where in particular

(i) R^5 and R^6 are H,

(ii) R^5 is H and R^6 is unsubstituted or substituted, branched or unbranched C_1-C_8-alkyl, aralkyl or

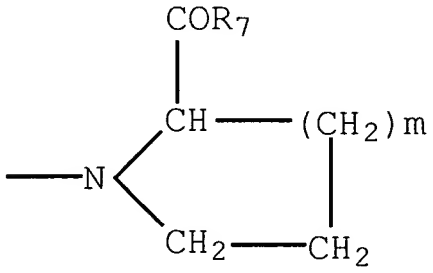
C_5-C_8-cycloalkyl,

(iii) R^5 and R^6 are in each case independently unsubstituted or substituted, branched or unbranched C_1-C_4-alkyl or

(iv) R^5 is H and R^6 is $-NH_2$ or is, in particular, an aryl-substituted or heteroaryl-substituted amino group,

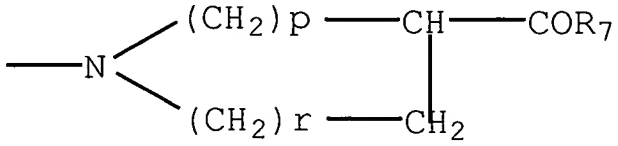
(v) R^5 is H or unsubstituted or substituted, branched or unbranched C_1-C_4-alkyl or R^6 is an amino acid residue, a peptide residue or a polypeptide residue,

(c) represents a group of the formula



in which m is the number 1 or 2 and in which one or more of the methylene groups are unsubstituted or substituted, with the group (c) being racemic or in D or L configuration, and R^7 has the meaning of R^1 in subsections (a), (b) and (f),

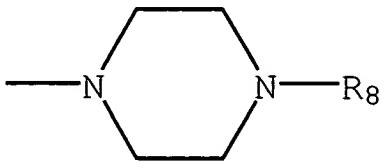
(d) represents a group of the formula



in which p=r=1, p=1 and r=2 or p=2 and r=1 and in which one or more of the methylene groups are unsubstituted or substituted and R^7 had the meaning of R^1 in subsections (a), (b) and (f),

(e) represents a piperidyl group which is unsubstituted or substituted in one of positions 2, 3 or 4, where a further aromatic or cycloaliphatic ring is optionally fused to the heterocycloaliphatic rings of the formulae (c), (d) and (e) in the 2, 3 position or the 3, 4 position relative to the heteroatom,

(f) represents a group of the formula



in which R^8 is

(i) unsubstituted or substituted C_1-C_6-alkyl or aryl,

(ii) saturated or unsaturated, unbranched or branched C_1-C_6 alkoxy or

(iii) unsubstituted or substituted phenoxy or benzyloxycarbonyl,

(g) represents an acyl radical of the formula -COX, where X is

(i) H, unsubstituted or substituted, unbranched or branched alkyl

(ii) unsubstituted or substituted aryl or heteroaryl, or

(iii) unsubstituted or substituted cycloalkyl,

(h) represents aralkyl in which the aromatic radical is unsubstituted or substituted,

(i) represents a carboxamide radical of the formula -CONR'R" , a thiocarboxamide radical, -CSNR'R" or an acetamide radical $-CH_2$-CONR'R" where

(i) R'and R" are H,

(ii) R' and R" are in each case independently C_1-C_4-alkyl,

(iii) R' is H and R" is C_1-C_4-alkyl,

(iv) R' is H and R" is aryl, or

(v) R' and R " constitute together with the nitrogen atom a heterocycloaliphatic ring having 5-7 ring members and possibly having a further heteroatom,

(j) represents SO_2-Y where Y is

(i) unsubstituted or substituted C_1-C_8-alkyl,

(ii) unsubstituted or substituted aryl or heteroaryl or O-aryl or 0-heteroaryl or

(iii) -NR'R", where R' and R" are in each case

independently H or C_1-C_3-alkyl,

(k) represents a cycloaliphatic unsubstituted or substituted ring having from 5 to 8 carbon atoms,

(l) represents an unsubstituted or substituted heteroaryl or heterocyclo-aliphatic radical,

(m) represents a functionalized alkyl radical of the formula $-(CH_2)_n-X$, where the alkyl chain is unbranched or branched, n = 1 to 8, and the functional radical X

(i) represents a hydroxyl group whose hydrogen atom is unsubstituted or substituted by C_1-C_4-alkyl-, aralkyl-, e.g. benzyl or phenyl-ethyl, aryl, C_1-C_4-hydroxyalkyl or acyl group CO-alkyl (C_1-C_6),

(ii) is a halogen atom

(iii) represents a tertiary amino group of the $-N(alk)_2$, where the alkyl groups have 1 to 3 carbon atoms and the nitrogen atom may belong to a heterocycloaliphatic ring having 5-7 ring members and possibly having a further heteroatom, S,] is selected from the group consisting of piperidine and piperazine, wherein said piperidine and said piperazine, independently, are each optionally substituted with C_1-C_8 alkyl, C_1-C_3 alkoxy, hydroxy, carboxyl, sulfonyl, nitro, cyano, oxo, halo or a combination thereof,

R^2 [represents unsubstituted or substituted] is 2, 4, 6 trisubstituted phenyl,

R^3 is H or branched or unbranched C_1-C_4-alkyl, and

n is 0 or 1,

or a salt of said compound.